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(54) Title: A PROCESS FOR PRODUCING CRYSTALLINE ATORVASTATIN CALCIUM

(57) Abstract: A factory scale process for producing crystalline atorvastatin calcium includes the step of drying the isolated product in a vacuum pan dryer. The vacuum pan dryer has an agitator which is continuously rotated at a speed of approximately 1 rpm. High quality material is routinely and consistently produced with reduced cycle time.

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A PROCESS FOR PRODUCING CRYSTALLINE ATORVASTATIN CALCIUM

Introduction

5 The invention relates to an improved process for producing crystalline atorvastatin calcium which is known by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt.

10 Atorvastatin is useful as a selective and competitive inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols such as cholesterol. The conversion of HMG-CoA to mevalonate is an early and rate-limiting step in cholesterol biosynthesis.

15 Atorvastatin as well as some of its metabolites are pharmacologically active in humans and are thus useful as a hypolipidemic and hypocholesterolemic agent. The liver is the primary site of action and the principal site of cholesterol synthesis. Clinical and pathological studies show that elevated plasma levels of
20 total cholesterol and associated triglycerides promote human atherosclerosis and are risk factors for developing cardiovascular disease.

United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-
25 1-yl) alkyl]-4-hydroxy-pyran-2-ones including trans (\pm)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

United States Patent Number 5,273,995, which is herein incorporated by
30 reference, discloses the enantiomer having the R form of the ring-opened acid of trans -5-(4-fluorophenyl)-2-(1-methylethyl)-N, 4-diphenyl-1-[(2-tetrahydro-4-

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hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid.

5 The above described atorvastatin compounds have been prepared by a superior convergent route disclosed in the following United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482 and 5,149,837 which are herein incorporated by reference and Baumann K.L., Butler D.E., Deering C.F., et al, *Tetrahedron Letters* 1992;33:2283-2284.

10 One of the critical intermediates disclosed in United States Patent Number 5,097,045 has also been produced using novel chemistry, as disclosed in United States Patent Number 5,155,251, which is herein incorporated by reference and Brower P.L., Butler D.E., Deering C.F., et al, *Tetrahedron Letters* 1992;33:2279-
15 2282.

United States Patent Numbers 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; 5,342,952; 5,298,627; 5,446,054; 5,470,981; 5,489,690; 5,489,691; 5,109,488; 5,969,156; US6,087,511; US5,998,663 and WO99/32434 which are
20 herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

It has been found that when the process for preparing atorvastatin calcium was scaled up to a commercial factory scale drying was slow and difficult to optimise.

25 It was also found that wet crystalline atorvastatin calcium was susceptible to possible break up with physical attrition and furthermore had a propensity to form rock hard clods on mixing.

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The object of the present invention is therefore to provide a process for producing crystalline atorvastatin calcium on a factory scale which routinely and consistently produces high quality material with reduced cycle time.

5 Statements of Invention

According to the invention there is provided a process for producing crystalline atorvastatin trihydrate hemi calcium salt comprising the steps of:-

10 reacting a mixture of atorvastatin lactone, methanol and methyl *tert*-butyl ether with sodium hydroxide to form the ring-opened sodium salt;

forming a product rich aqueous layer and an organic layer comprising methyl *tert*-butyl ether containing impurities;

15 removing the organic layer comprising methyl *tert*-butyl ether containing impurities;

extracting the product rich aqueous layer with methyl *tert*-butyl ether;

20 adding an extra charge of methyl *tert*-butyl ether to a vessel containing the product rich aqueous layer in an amount of at least 1% w/v of the contents of the vessel;

25 sealing the reaction vessel;

heating the contents of the sealed reaction vessel to 47 to 57°C in the presence of the extra charge of methyl *tert*-butyl ether which saturates the crystallisation matrix on heating;

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adding calcium acetate hemihydrate to the sealed reaction vessel to form atorvastatin trihydrate hemi calcium salt; and

drying the isolated product in a vacuum pan dryer having an agitator which is continuously rotated at a speed of from 0.5 to 2rpm.

It has been surprisingly found that this continuous agitation at a very low speed provides optimum drying conditions with very significant increased throughput while avoiding clod formation and particle attrition. As more solvents are evaporated from the cake in the dryer the crystals are increasingly susceptible to attrition. The process ensures that no break-up occurs with physical attrition. Clod formation on mixing is also avoided.

In a particularly preferred embodiment of the invention the agitator is substantially continuously rotated at a speed of approximately 1rpm. This provides reduced drying time while ensuring uniform drying of the crystals and avoidance of clod formation and particle attrition. We have found that this uniform drying ensures that all water is evenly removed from the cake in the dryer.

In a preferred embodiment the vacuum in the pan dryer is maintained at from -0.80 to -0.99 bar.

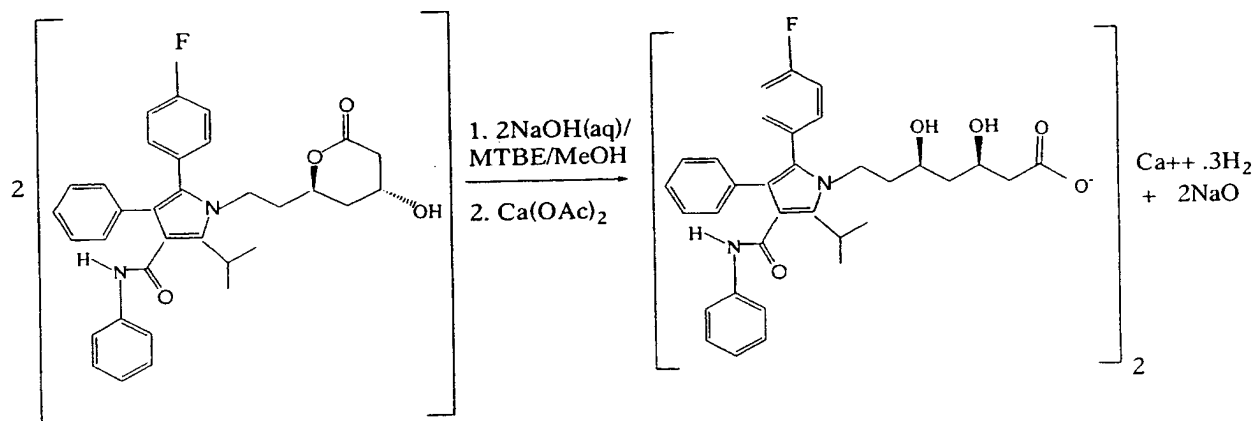
Preferably the isolated product is dried over a period of from 1 to 4 days, ideally over a period of from 1 to 2 days.

Detailed description

Atorvastatin lactone is saponified in a water/methyl alcohol/methyl *tert*-butyl ether (2-methoxy-2-methyl-propane; *tert*-butyl methyl ether) mixture with sodium hydroxide. The aqueous layer containing the sodium salt of atorvastatin is washed

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with methyl *tert*-butyl ether to remove small quantities of process impurities. A small aliquot of methyl *tert*-butyl ether is added to the crystallisation matrix. Sodium-to-calcium salt metathesis with concurrent crystallisation is accomplished by the slow addition of an aqueous calcium acetate solution to the sodium salt solution. To ensure crystallisation simultaneous with addition, the reaction mixture is seeded with crystalline atorvastatin shortly after the start of the calcium acetate addition. The product is isolated by filtration and, after washing with water/methyl alcohol and water is centrifuged and vacuum dried before milling to give crystalline atorvastatin as the trihydrate. The reaction scheme is shown below.



Scheme 1

We have surprisingly found that the drying of atorvastatin calcium has a sensitive window of moisture content of approximately 6% w/v where the drying has to proceed slowly in order to prevent the particles from breaking down. As more solvents are evaporated from the cake in the dryer, especially around 6% water, the particles are increasingly susceptible to attrition.

We have found that continuous agitation at approximately 1rpm significantly reduces the drying time compared to an intermittent agitation technique, thereby increasing drying capacity while ensuring that the final dried product is within a

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consistent range for particle size and bulk density. This is in complete contrast to continuous medium speed agitation which results in clod formation and the risk of physical attrition and intermittent agitation which substantially increases the required drying time. Continuous agitation at 0.5 to 2 rpm is outside the normal design operating range of agitated pan dryers.

Example 1

250kg atorvastatin lactone prepared as described in US 5,273,995 the entire contents of which are incorporated by reference, 1028kg methyl *tert*-butyl ether and 496kg of methanol are charged to a 6000 litre glass lined reaction vessel. The reaction mixture is agitated and heated to about 30°C to dissolve the lactone. When the lactone is dissolved, approximately 3200 litres of caustic solution is added (19kg of sodium hydroxide 97.5% dissolved in 3165 litres of deionised water). The contents of the vessel are heated to 47 to 57°C and agitated for at least 45 minutes.

After cooling to 25 to 35°C under an inert atmosphere the contents are allowed to settle and the organic layer is discarded. 765kg methyl *tert*-butyl ether is charged to the aqueous layer, the contents mixed and allowed to settle. The organic layer is discarded.

63kg of extra methyl *tert*-butyl ether is charged to the product rich aqueous layer in the reaction vessel which is then sealed. The contents of the sealed reaction vessel are heated to 47 to 57°C maintaining a pressurised system.

A solution of calcium acetate (40kg calcium acetate hemihydrate in 1365 litres deionised water) is transferred to the pressurised vessel. Shortly after commencement of the calcium acetate addition the transfer is stopped and atorvastatin trihydrate hemi calcium salt seed, prepared as described in US5,969,156 which is herein incorporated by reference, is introduced.

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5 A seed slurry is prepared by charging 37 litres deionised water and 13kg methanol to a stainless steel make-up/delivery vessel. The solvent mixture is agitated by rocking the vessel back and forth on its cradle. 3.6kg atorvastatin calcium seed crystals are then charged to the solvent mixture. The contents of the delivery vessel are mixed by rocking until a seed slurry is formed. Sufficient pressure is applied to the make-up/delivery vessel so that its pressure is higher than that of the reaction vessel. The make-up/delivery vessel is attached to the reaction vessel via a flexible hose and the seed slurry is charged rapidly over 2 to 3 minutes, under pressure, into the reaction vessel.

After the addition of the seed slurry the calcium acetate addition is immediately resumed to complete the calcium transfer.

15 The product cake is washed first with a methanol/water solution followed by a water wash.

Example 2: Drying of atorvastatin calcium

20 The wet product prepared in Example 1 is loaded into a stainless steel continuous agitation pan dryer such as a Guedu Pan Dryer. A full vacuum of from -0.80 to -0.99 bar is applied, the jacket of the dryer adjusted to 60 to 70°C and the product dried with slow continuous agitation at approximately 1rpm for at least 24 hours, preferably for from 1 to 4 days, ideally 1 to 2 days.

25 The dry product is then loaded into clean poly-lined drums.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

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Claims

1. A factory scale process for producing crystalline atorvastatin trihydrate hemi calcium salt comprising the steps of:-

5

reacting a mixture of atorvastatin lactone, methanol and methyl *tert*-butyl ether with sodium hydroxide to form the ring-opened sodium salt;

10

forming a product rich aqueous layer and an organic layer comprising methyl *tert*-butyl ether containing impurities;

removing the organic layer comprising methyl *tert*-butyl ether containing impurities;

15

extracting the product rich aqueous layer with methyl *tert*-butyl ether;

20

adding an extra charge of methyl *tert*-butyl ether to a vessel containing the product rich aqueous layer in an amount of at least 1% w/v of the contents of the vessel;

sealing the reaction vessel;

25

heating the contents of the sealed reaction vessel to 47 to 57°C in the presence of the extra charge of methyl *tert*-butyl ether which saturates the crystallisation matrix on heating;

30

adding calcium acetate hemihydrate to the sealed reaction vessel to form atorvastatin trihydrate hemi calcium salt; and

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drying the isolated product in a vacuum pan dryer having an agitator which is continuously rotated at a speed of from 0.5 to 2rpm.

2. A process as claimed in claim 1 wherein the agitator is substantially
5 continuously rotated at a speed of approximately 1rpm.
3. A process as claimed in claim 1 or 2 wherein the vacuum in the pan dryer is maintained at from -0.80 to -0.99 bar.
- 10 4. A process as claimed in any preceding claim wherein the isolated product is dried over a period of from 1 to 4 days.
5. A process as claimed in any preceding claim wherein the isolated product is dried over a period of from 1 to 2 days.

15

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 97 03958 A (WARNER LAMBERT CO ; MCKENZIE ANN T (US)) 6 February 1997 (1997-02-06) examples 1,2	1-5

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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